

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Rea et al.

Serial No.: 09/666,430

Filed: September 21, 2000

For: DENDRITIC CELL ACTIVATED IN
THE PRESENCE OF GLUCOCORTICOID
HORMONES ARE CAPABLE OF
SUPPRESSING ANTIGEN-SPECIFIC T
CELL RESPONSES

Confirmation No.: 6289

Examiner: G. Ewoldt, Ph.D.

Group Art Unit: 1644

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BRIEF ON APPEAL

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Sirs:

This brief is submitted as a single copy pursuant to 37 C.F.R. § 41.37 and in the format required
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(1) REAL PARTY IN INTEREST

The real party in interest in the present pending appeal is Leids Universitair Medisch Centrum (University of Leiden Medical Center), assignee of the pending application as recorded with the United States Patent and Trademark Office on October, 2000, at Reel 011197, Frame 0136.

(2) RELATED APPEALS AND INTERFERENCES

Neither the Appellants, the Appellants' representative, nor the Assignee is aware of any pending appeal or interference which would directly affect, be directly affected by, or have any bearing on the Board's decision in the present pending appeal.

(3) STATUS OF THE CLAIMS

Claims 2 through 39 were cancelled without prejudice or disclaimer

Claims 1 and 40 through 81 stand rejected.

No claims are allowed.

The rejections of claims 1 and 40 through 81 are being appealed.

(4) STATUS OF AMENDMENTS

The appellants' amendments, filed April 27, 2005 in conjunction with a Request for Continued Examination, have been entered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention provides means and methods for immunotherapy. The invention provides immune cells and methods to generate them, where the immune cells have the capacity, at least in part, to reduce an immune response in a host. *See*, Specification at ¶¶ 18-29. In one aspect, the invention provides a method for generating a dendritic cell with the capacity to tolerize a T-cell for the antigen the T-cell is specific for. *See*, Specification at ¶ 18. More specifically, one aspect of the invention relates to culturing blood monocytes from a subject to differentiate into dendritic cells, activating the dendritic cells in the presence of a glucocorticoid hormone, and loading the activated dendritic cell with an antigen that a T-cell is specific for. *See*, Specification at ¶¶ 18-20, 22, 30, and 35.

As set forth in 37 C.F.R. 41.73 (c) (1) (vii), every means plus function claim must be identified and the structure materials or acts described in the specification corresponding to each claimed function must be set forth with reference to the specification. The current application contains a single means plus function claim, to wit: claim 1. The relevant means plus function language of claim 1 recites “activating said dendritic cells with a means for reducing IL-12p40 production by said dendritic cells.”

The specification, in Example 3 (¶ 34), clearly indicates that dexamethasone, a known compound, has the ability to reduce reducing IL-12p40 production by a dendritic cell, and is thus a disclosed means to accomplish this function. Further, the Examiner, in the Office Action mailed July 26, 2005, at Page 5, agrees dexamethasone is a disclosed means for the function of reducing IL-12p40 production by said dendritic cells.

(6) GROUND OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 1, 46, and 55 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement?

B. Whether claims 40-81 are unpatentable under 35 U.S.C. § 112, first paragraph, as constituting “new matter?”

C. Whether claims 1 and 40-81 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement?

(7) ARGUMENT

(i) 35 U.S.C. § 112, first paragraph, written description

Claims 1, 46, and 55 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement.

As amended, independent claim 1 recites “a method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host, said method comprising: culturing peripheral blood monocytes from said host to differentiate into dendritic cells; activating said dendritic cells with a means for reducing IL-12p40 production by said dendritic cells; loading said dendritic cells with an antigen against which said T-cell response is to be reduced; and forming a pharmaceutical composition comprising said loaded, activated dendritic cells for administration to said host.”

As amended, dependent claim 46, including the element of independent claim 40, recites “a method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host against an antigen, said method comprising: culturing peripheral blood monocytes from said host to differentiate into dendritic cells; activating said dendritic cells with a glucocorticoid capable of activating a glucocorticoid receptor; bringing said dendritic cells into contact with an antigen against which said T-cell response is to be reduced; and forming a pharmaceutical composition comprising said loaded, activated dendritic cells; wherein activating said dendritic cells with said substance capable of activating the glucocorticoid receptor comprises activating said dendritic cells such that said dendritic cells secrete interleukin-10.”

As amended, dependent claim 55, including the elements of independent claim 51 and intervening claim 51, recites “a method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen, comprising: providing said dendritic cell with a substance capable of activating a glucocorticoid receptor; activating said dendritic cell; and providing said dendritic cell with said antigen, wherein said dendritic cell is capable of tolerizing a T-cell for said antigen; wherein providing said dendritic cell with the substance capable of activating a glucocorticoid receptor is in vitro; and wherein said substance capable of activating the glucocorticoid receptor enhances secretion of IL-10 by said dendritic cells.”

Alleged Basis of the Rejections

As to claims 1, 46, and 55 the Examiner, in the Office Action mailed May 21, 2003 at Page 4, alleges that

There is insufficient written description to show that Applicant was in possession of “means for reducing IL-12p40 production by said dendritic cell” or “means for

causing said dendritic cell to secrete IL-10 in vitro,” other than dexamethasone. As said “means” comprises an unknown genus of indeterminate size, one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus. Likewise the specification discloses no specific “antigen(s) against which said T-cell response is to be reduced.” Again, given the indeterminate size of the claimed “antigen” genus . . . one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus.

In addition, the Examiner alleges that “the single substance capable of activating a glucocorticoid receptor disclosed in the specification, *i.e.*, Dex, is not considered to be a representative number of examples of the claimed genus of all substances capable of activating a glucocorticoid receptor.” Office Action mailed December 27, 2004 at Page 6.

Further, the Examiner asserts that “a representative number of examples is required.” *Id.* The Examiner further alleges that “a single example is not a representative number of examples of the genus in this instance.” *Id.*

Adequate Written Description For The Means Plus Function Element Of Claim 1 Exists In The Specification

35 U.S.C. § 112, Paragraph 6 relates that

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

“The USPTO must apply 35 U.S.C. 112, sixth paragraph in appropriate cases, and give claims their broadest reasonable interpretation, in light of and consistent with the written description of the invention in the application. *In re Donaldson Co.*, 16 F.3d 1189, 29 USPQ2d 1845 (Fed. Cir. 1994). Under MPEP §2181(I), a claim element will be interpreted to invoke 35 U.S.C. 112, sixth paragraph, if it meets the following 3-prong analysis:

- (A) the claim limitation must use the phrase “means for” or “step for;”
- (B) the “means for” or “step for” must be modified by functional language; and

(C) the phrase “means for” or “step for” must not be modified by sufficient structure, material, or acts for achieving the specified function.

Claim 1 is the only claim at issue that contains a means plus function element. Specifically, claim 1 recites, in part, “activating said dendritic cells with a means for reducing IL-12p40 production by said dendritic cells.” Prong (A) of the 3-prong test is clearly met as the claim clearly recites “means for.” Prong (B) of the 3-prong test is also met as the means for is modified by function language, to wit: “means for reducing IL-12p40 production by said dendritic cells.” Lastly, prong (C) of the 3-prong test is met as the “means for” recited in claim 1 is not modified by any structure, material, or acts for achieving the specified function. As such, claim 1 invokes clearly invokes 35 U.S.C. 112, sixth paragraph.

In rejecting claim 1, the Examiner alleges, that “as said ‘means’ comprises an unknown genus of indeterminate size, one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus.” Office Action mailed 21, 2003 at Page 4. However, the Examiner’s assertion regarding the size of the genus is in direct contravention to 35 U.S.C. § 112, sixth paragraph. As noted above, 35 U.S.C. § 112, sixth paragraph provides, in part, that “such claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.” As such, the “means” recited in claim 1 cannot be construed as being of indeterminate size as the means must be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Further the MPEP at § 2163 (II)(3)(a) indicates that “A means- (or step) plus-function claim is adequately described under 35 U.S.C. § 112, paragraph 1, if the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a means- (or step) plus function limitation.”

The Examiner acknowledges that dexamethasone (dex) is a disclosed means for reducing IL-12p40 production by dendritic cells. Office Action mailed July 26, 2005 at Page 5. In so noting, the Examiner asserts that “it remains the Examiner’s position that Dex is not a sufficiently representative number of means for reducing IL-12p40 production by a dendritic cell.” *Id.* However, appellants are not required to provide an adequate number of species to define the genus. As the MPEP and the Federal Circuit have pointed out, written description is

satisfied if the specification adequately links a particular material to the function recited. *See In Re Donaldson, supra*. The Examiner, as noted above, agrees that Dex is a particular material that has been adequately linked to the function recited. Further, the specification, in Example 3 (§ 34), indicates that dexamethasone, a known compound, has the ability to reduce reducing IL-12p40 production by a dendritic cell. As such, appellants respectfully submit that the specification provides adequate written description of a means for reducing IL-12p40 production by a dendritic cell and that the “means” recited in claim 1 does not comprise an unknown genus of indeterminate size. Consequently, appellants respectfully request that the rejection of claims 1 under 35 U.S.C., first paragraph, for lack of written description for recitation of the term “means” be withdrawn and the claim allowed.

The Term “Antigen” Does Not Give Rise To A Genus of Indeterminate Size In Claims 1, 46, and 55

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was “ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998). Further, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

The Examiner alleges, at page 6 of the Office Action mailed December 27, 2004, that “a representative number of examples is required” to establish written description. And that “[s]aid representative number can only be established in relation to the genus in question. *Id.* Appellants respectfully submit that the Examiner’s requirement for a representative number of examples is contrary to established examination procedure. MPEP § 2163(II) (3) (a) (ii) provides that:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and /or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function or structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claim genus. *See Regents of the University of California v. Eli Lilly*, 199 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

As such, appellants respectfully assert that Examiner is mistaken in his assertion that “a representative number of examples is required,” as established case law and the MPEP provide numerous alternatives to providing a representative number of species.

The Examiner further alleges that “the specification discloses no specific ‘antigen(s) against which said T-cell response is to be reduced.’” Office Action mailed May 21, 2003 at Page 4. Appellants respectfully submit that which antigen a T-cell response is to be reduced is subjective in nature. The selection of the antigen is a decision of the practitioner of the invention and any antigen can be selected for use in practicing the present invention. Further, the appellants provide two examples of antigens to which were tested to see if a T-cell response to them was reduced. Specifically, Example 4 of the specification (§ 35) shows the reduction of a T-cell response to the antigens hsp65 protein and p3-13. As such, given that the appellants selected hsp65 and p3-13 as antigens to which a T-cell response was to be reduced, and further demonstrated a reduction in T-cell response to these two antigens, appellants respectfully submit that the specification does disclose at least two examples of antigens to which a T-cell response is to be reduced.

To the extent that the Examiner is alleging that the appellants do not have possession of the genus defined by the term “antigen,” appellants respectfully submit that one of skill in the art would conclude that appellants had possession of “antigens” as the genus encompassed by the term is well known in the art, examples of antigens are well known in the art, and exemplary “antigens” are reduced to practice in the examples as well as in the Declaration of Rienk Offiringa.

“Claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds.” *In re Herschler*, 591 F.2d 693, 702, 200 USPQ 711, 714 (CCPA 1979). In decision of the CCPA in *In re Herschler*, it was found that a single example of a steroid was sufficient to provide written description for the entire genus of steroids as the “[a]ppellant’s invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties.” *Id* at 701. Further the court noted that “[w]e see nothing in patent law which requires appellant to discover which of all those salts have such properties and will function properly in his combination.” *Id*.

Appellants respectfully submit that the instant case sits on all four corners of the *In re Herschler* decision. In the present case, the applicant is claiming a specific combination of method steps in claims 1, 46, and 55 of which the selection of an antigen is only auxiliary to the claimed methods. As in *In re Herschler*, the invention defined by the present claims is not that specific antigens have a particular property or are novel in any way. The novelty of the claimed invention resides in the combination of all of the method steps.

Further, as in *In re Herschler*, antigens are known chemical compounds. Antigen is a term that is well defined in the art. The courts have recognized the definition of an antigen as a “foreign molecule of sufficient size can act as a stimulus for antibody production.” *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1368 (Fed. Cir. 1986). As such, the term “antigen” is well known in the art. Further, at least hundreds of antigens are known in the art. The following is a truncated exemplary list of know antigens: influenza viruses, immunoglobulin E (IgE) which indicates allergic reaction, human chorionic gonadotropin (HCG) which indicates pregnancy, and prostatic acid phosphatase (PAP) which indicates prostate cancer. *Id.* at 1370.

In addition, the specification and Declaration of Rienk Offringa, which is of record in the present case, provides examples of antigens that may be used in accordance with the present invention. Specifically, Example 2 of the specification (§ 33) indicates the uptake of the antigens FITC-BSA and FITC-mannosylated BSA. Further, Example 4 of the specification (§ 35) shows the use of the hsp65 protein and the specific peptide epitope p3-13 as antigens. Last, the Declaration of Rienk Offringa, at page 9, indicates the use of C57BL/6 alloantigens and conA as antigens. As such, the specification and the Declaration of Rienk Offringa show the use of no less than six antigens.

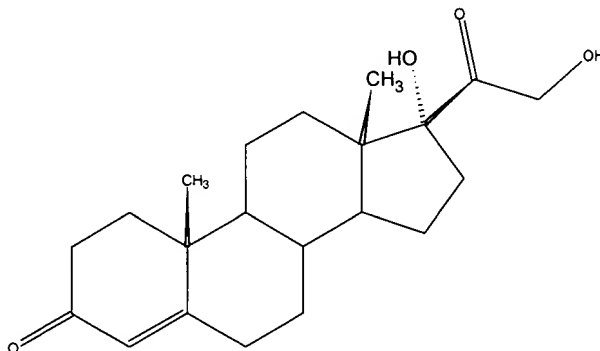
As directed by *In re Herschler*, where claims are drawn to the use of known compounds in a manner auxiliary to the invention, as is the case in the present application, the corresponding written description needs be only so specific as to lead one of ordinary skill in the art to that class of compounds. Appellants respectfully submit, as the term antigen is directly used in the claims, antigens are well known and characterized in the art, and as the specification and Declaration of Rienk Offringa provide examples of antigens, one of skill in the art would be lead to use that class of compounds. As such, given direction of *In re Herschler*, appellants respectfully submit that the phrase “antigen(s) against which said T-cell response is to be reduced” and specifically the term “antigen” have adequate written description in the specification. Consequently, appellants respectfully request that the rejection of claims 1, 46, and 55 under 35 U.S.C., first paragraph, for lack of written description be withdrawn and the claims allowed.

Substances Capable Of Activating A Glucocorticoid Receptor Recited in Claims 46, and 55 Are Well Known In The Art

In rejecting claims 46 and 55 the Examiner alleges that:

The single substance capable of activation a glucocorticoid receptor disclosed in the specification, *i.e.*, Dex, is not considered to be a representative number of examples of the claimed genus of all substances capable of activating a glucocorticoid receptor. Applicant is reminded, as set forth previously, that the term must be given its broadest reasonable interpretation, such as set for the in *Stedman's Medical Dictionary* (2002) wherein glucocorticoid is defined as “any steroid-like compound capable of significantly influencing intermediary metabolism.”

As noted *supra*, a representative number of examples of the claimed genus is not required. *Eli Lilly* at 1559. An additional option for compliance with the written can be provided by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties. *Id.* As is well known in the art, glucocorticoids (*e.g.* chemicals capable of activating the glucocorticoid receptor) have a common base chemical structure; to wit:



Goodman *et al.*, Goodman and Gilman's The Pharmacological Basis of Therapeutics, (Seventh Ed.) Ch 23 Adrenocorticotrophic Hormone: Adrenocortical Steroids and their Synthetic Analogs: Inhibitors of Andrenocortical Steroid Biosynthesis, page 1464. Further, the use of glucocorticoids in the present invention is discussed in each of ¶¶ 18-20, As such, appellants respectfully submit that adequate written description of substances capable of activating a glucocorticoid receptor exists as the use of glucocorticoids is discussed in multiple locations in the specification and glucocorticoids are a well known class of compounds with common chemical properties. Consequently, appellants respectfully request that the rejection of claims 46, and 55 under 35 U.S.C., first paragraph, for lack of written description be withdrawn and the claims allowed.

In addition, as noted *supra*, claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds." *In re Herschler*, 591 F.2d at 702. In decision of the CCPA in *In re Herschler*, it was found that a single example of a steroid was sufficient to provide written description for the entire genus of steroids as the '[a]ppellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties." *Id* at 701. Further the court noted that "[w]e see

nothing in patent law which requires appellant to discover which of all those salts have such properties and will function properly in his combination.” *Id.*

Appellants respectfully submit that the instant case sits on all four corners of the *In re Herschler* decision. In the present case, the applicant is claiming a specific combination of method steps in claims 46, and 55 of which the use of a specific substance capable of activating a glucocorticoid receptor is only auxiliary to the claim methods. As in *In re Herschler*, the invention defined by the present claims is not that specific glucocorticoids are novel in any way, the novelty of the claimed invention resides in the combination of all of the method steps.

Further, as in *In re Herschler*, compositions capable of activating a glucocorticoid receptor are well known chemical compounds. Goodman and Gilman defines a glucocorticoid as 21 carbon steroids with the general structure illustrated *supra*. Goodman *et al.*, at page 1464. As such, substances capable of activating the glucocorticoid receptor (*i.e.* glucocorticoids) are well known in the art. Further, multiple examples of glucocorticoids are known in the art. The following is a truncated exemplary list of known glucocorticoids: betamethasone, cortisone, dexamethasone, fludrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, and triacinelone. *Id.* at page 1475. Only minor differences distinguish these glucocorticoids including the presence of a double bond at the 1-2 position, and the presence or absence of various small auxiliary groups at positions 6, 9, 11, and 16. *Id.* at page 1474.

In addition, the specification provides an example of a glucocorticoid (dexamethasone) that may be used in accordance with the present invention to activate a glucocorticoid receptor. Specifically, Examples 1-4 of the specification disclose use of dexamethasone at a dosage 1000 times the level needed to fully activate the glucocorticoid receptor (*see* ¶ 38 of the specification and Cronstein *et al.* (1992) Proc. Natl. Acad. Sci. USA 89:9991-9995 at Figures 1 and 3.)

As directed by *In re Herschler*, where claims are drawn to the use of known compounds in a manner auxiliary to the invention, as is the case in the present application, the corresponding written description needs be only so specific as to lead one of ordinary skill in the art to that class of compounds. Appellants respectfully submit, as the use of a substance capable of activating a glucocorticoid receptor is disclosed in the specification, substances capable of activating a glucocorticoid receptor (*i.e.* glucocorticoids) are well known and characterized in the art, and as the specification provides a specific example and use of such a substance, one of skill in the art

would be lead to use that class of compounds. As such, given direction of *In re Herschler*, appellants respectfully submit that the phrase "substance capable of activating a glucocorticoid receptor" has adequate written description in the specification. Consequently, appellants respectfully request that the rejection of claims 46, and 55 under 35 U.S.C., first paragraph, for lack of written description be withdrawn and the claims allowed.

(ii) 35 U.S.C. § 112, first paragraph, written description, new matter

Claims 40-81 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly constituting new matter.

Specifically, the Examiner alleges, in the Office Action mailed December 27, 2004, at page 7, that:

The specification and the claims as originally filed do not provide support of the invention as now claimed, specifically:

A) A substance capable of activating a glucocorticoid receptor (claims 40 and 51-55)

B) A method for preparing an isolated dendritic cell, said method comprising:
isolating peripheral blood monocytes from a subject;
culturing the peripheral blood monocytes to differentiate into dendritic cells;
activating the dendritic cells with a glucocorticoid;
loading the dendritic cells with and antigen; and
isolating said loaded, activated dendritic cells (claim 56)

C) The method according to claim 56, wherein the antigen comprises an allogenic antigen (claim 59)

D) A method for obtaining a dendritic cell capable of tolerizing a T-cell in a graft or transplant recipient (claims 64 and 65).

Regarding A) the specification supports binding but not activating.

Regarding B) the specification does not disclose this generic method for preparing any type of isolated DC.

Regarding C) the specification does not disclose the generically-claimed method employing a generic allogenic antigen.

Regarding D) the specification discloses only tolerizing T cells to an antigen and not tolerzing a generic T-cell or tolerzing a T-cell in a graft or transplant recipient.

The Examiner further alleges, in the Office Action mailed July 26, 2006, at pages 7-9, that the following new claims also constitute new matter, noting that:

- A) A method for preparing a pharmaceutical composition for reducing an unwanted T-cell response to an antigen in a host, said method comprising:
culturing peripheral blood monocytes from said host to differentiation into dendritic cells *in vitro*;
contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced, thereby loading said dendritic cells with the antigen;
contacting said dendritic cells with dexamethasone;
activating the CD40 receptor on said dendritic cells; and
forming a pharmaceutical composition comprising said loaded, activated dendritic cells (claim 69).
- (B) The method of claim 69 comprising the additional limitation of claims 70-76.
- (C) A method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen, the method comprising:
contacting a dendritic cell with dexamethasone *in vitro*;
activating the dendritic cell through the CD40 receptor; and
contacting the dendritic cell with an antigen, thereby loading the dendritic cell with the antigen, and forming a dendritic cell capable of tolerizing a T-cell for the antigen (claim 77).
- (D) The method of claim 77 comprising the additional limitations of claims 78-81.
- (E) The methods of claims 43 and 75 comprising incubating DCs with a peptide antigen.
- (F) The method of claim 53 comprising providing a precursor of a DC.
- (G) The method of claim 58 comprising loading DCs with an antigen defined by the response of a T cell.
- (H) The method of claims 61, 65, 68, 78, 80, and 81 comprising DCs derived from a graft or transplant donor.

A review of the specification shows no support for the specific order of the steps in claim 69, *e.g.*, contacting the cells with antigen before contacting the DCs with Dex before activating the DCs. Nor does the specification support the specific order of the steps in claim 77, *e.g.*, contacting the cells with Dex before activating the DCs before contacting the DCs with antigen.

Regarding (E), the specification does not disclose peptide antigens and original claim 9 discloses only synthetic peptides.

Regarding (F), the specification does not disclose "a precursor of a DC."

Regarding (G), the specification does not disclose "an antigen defined by the response of the T cell."

Regarding (H), the specification does not disclose "DCs derived from a graft or transplant donor."

To comply with the written description require of 35 U.S.C. § 112, first paragraph, each claim limitation must be expressly, implicitly, or inherently support in the originally filed disclosures. MPEP § 2163(II)(A)(3)(b). Further, the subject matter of the claim need not be described literally, *in haec verba*, in order for the disclosure to comply with the written description requirement. MPEP § 2163.02.

As To Claim 40 And 51-55, Activating A Glucocorticoid Has Support In The Specification

As noted *supra*, compliance with the written description requirement can be met if a claim limitation is implicitly or inherently supported in the originally filed disclosures. MPEP § 2163(II)(A)(3)(b). The Examiner indicates, in the Office Action mailed December 27, 2004, at page 7, that “the specification supports binding [of Dex to a glucocorticoid receptor] but not activating [a glucocorticoid receptor with Dex].” However, appellants respectfully submit that the agreed upon binding of Dex to the glucocorticoid receptor implicitly and inherently results in its activation. That Dex activates the glucocorticoid receptor is well known in the art. For example, Cronstein *et al.* indicate that “antagonism by dexamethasone . . . is a specific instance of the general biological principle that the glucocorticoid receptor is a hormone dependent regulator of transcription. Cronstien B.M., Kimmel S.C, Levin R.I., Martinuik F., and Weismann G: A mechanism for the anti-inflammatory effect of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. (1992) Proc. Natl. Acad. Sci. USA 89:9991-9995 at the abstract. Further, the experiments of Cronstein *et al.* reached a maximal effect on the glucocorticoid receptor at 10nM dexamethasone. *Id.* at Figures 1 and 3. Appellants, as noted in ¶ 38 of the specification, use 10mM dexamethasone, 1000 times the level indicated by Cronstein *et al.* to achieve maximal activation of the glucocorticoid receptor. Last, the Examiner acknowledges that dexamethasone is capable of activating a glucocorticoid receptor, to wit: “[a]pplicant is advised that the single substance capable of activating receptor disclosed in the specification, *i.e.*, dex” Office Action mailed December 27, 2004, at Page 6. As such, given the known ability of dexamethasone to activate the glucocorticoid receptor, the amount of dexamethasone used by the appellants in their examples to activate the glucocorticoid

receptor, and the statement by the examiner that dexamethasone is capable of activating the glucocorticoid receptor, one of skill in the art would conclude that the specification at the very least implicitly and inherently provides written description for the activation of the glucocorticoid receptor. Consequently, appellants respectfully request that the rejection of claims 40, and 51-55 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claims allowed.

The Specification Discloses The Method of Claim 56

As noted *supra*, claim 56 recites:

A method for preparing an isolated dendritic cell, said method comprising:
isolating peripheral blood monocytes from a subject;
culturing the peripheral blood monocytes to differentiate into dendritic cells;
activating the dendritic cells with a glucocorticoid;
loading the dendritic cells with and antigen; and
isolating said loaded, activated dendritic cells.

Appellant respectfully submit that support for claim 56 can be found throughout the specification. Specifically, original claim 1 provides support for many of the steps recited in claim 56. Original claim 1 recites:

A method for preparing a pharmaceutical composition for reducing an unwanted Tcell response in a host, comprising
culturing peripheral blood monocytes from said host to differentiate into dendritic cells,
activating said dendritic cells in the presence of a glucocorticoid hormone and
loading said dendritic cells with an antigen against which said Tcell response is to be reduced.

The step of “culturing peripheral blood monocytes from said host to differentiate into dendritic cells” in original claim 1 inherently and implicitly provides written description of the steps of “isolating peripheral blood monocytes from a subject” and “culturing the peripheral blood monocytes to differentiate into dendritic cells” that are recited in claim 56. The step of claim 1 and the steps of claim 56 amount to the same act as they give the same result using the same steps but are laid out in slightly different language. Further support for these steps of claim 56 are found in ¶ 36 of the specification. Specifically, that paragraph relates “[h]uman

[peripheral blood monocytes precursors] from healthy donors, [were] isolated.” Further ¶ 36 of the specification relates that “[i]mmature DC were generated from peripheral blood monocytes precursors.” Thus, appellants respectfully submit that support for the claim 56 steps of “isolating peripheral blood monocytes from a subject” and “culturing the peripheral blood monocytes to differentiate into dendritic cells” are at least supported in original claim 1 and in ¶ 36 of the specification. Other support for these steps can be found throughout the specification.

The step of “activating the dendritic cells with a glucocorticoid” of claim 56 also has support throughout the specification. In particular, activating the heretofore unknown developmental pathway of dendritic cells with glucocorticoid is described in ¶¶ 18-22.

Further, the step of “loading the dendritic cells with an antigen” is supported throughout the specification. In particular, as noted *supra*, original claim 1 specifically recites “loading said dendritic cells with an antigen against which said T-cell response is to be reduced.” As such, this particular method step is at least supported as the specific step is found in original claim 1.

Last, the step of “isolating said loaded, activated dendritic cells” is supported throughout the specification. In particular, ¶ 25 of the specification provides for “an isolated functionally modified T-cell obtainable by a method according to the invention. As such, appellants respectfully submit that the last step of claim 56 is explicitly described in at least ¶ 25 of the specification.

In view of the foregoing, appellants respectfully submit that each and every element of claim 56 is supported in the specification and originally filed claims. Consequently, appellants respectfully request that the rejection of claim 56 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claim allowed.

Support Exists In The Specification For Claim 59

As noted *supra*, claim 59 stands rejected as constituting new matter. Specifically, the Examiner, at Page 7 of the Office Action mailed December 27, 2004, notes that “[t]he cited paragraphs do not disclose the limitations of the claim, *e.g.*, the preparation of a generic isolated DC employing peripheral blood monocytes and an allogeneic antigen. Note that paragraph 35 does disclose an alloantigen, but the disclosure is made in a specific example and cannot support a generic method.”

Claim 59 recites “[t]he method according to claim 56, wherein the antigen comprises an allogenic antigen.”

By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. MPEP § 2163.07(a); *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971). The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *Id.*

As noted *supra*, support exists in the specification for the term “antigen.” As would be understood by one of skill in the art, “antigen” is a broad term that encompasses generally many different subtypes of antigens. Further, appellants are entitled to the broadest reasonable interpretation of the language. *See e.g., In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). As would be understood by one of skill in the art, given the broadest reasonable interpretation of the term “antigen,” the use of antigens as described in the specification inherently has the properties all subtypes of antigens. As such, appellants respectfully submit that adequate written description for the term “allogenic antigen” exists in the specification.

Further, the courts have defined allogenic as “[i]ntraspecies variance at a particular gene locus. Referring to genetic variants within a species.” *Johns Hopkins University v. CellPro*, 894 F.Supp. 819, 825 (D.Del.,1995). As is well known in the art, antigenically distinct grafts or transplants may give rise, through allogenic antigens, to an unwanted immune response that characterizes one aspect of graft-versus-host or host-versus-graft disease. The specification, at ¶¶ 7, 18, and 29 specifically note the use of the invention in treating these diseases. Thus, one of skill in the art would understand that in order to combat these diseases as disclosed in the specification, the antigens described in the specification must inherently include allogenic antigens.

As such, appellants respectfully submit that the term “antigen,” given its broadest reasonable interpretation inherently describes allogenic antigens, and that one of skill in the would understand that allogenic antigens are inherently disclosed in the specification as antigens usefully in the disclosed methods for treating graft-versus-host or host-versus-graft disease.

Consequently, appellants respectfully request that the rejection of claim 59 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claims allowed.

Claims 64 And 65 Specifically Recite Tolerizing A T-Cell To An Antigen

As noted *supra*, claims 64 and 65 stand rejected as constituting new matter. Specifically, the Examiner, at Page 7 of the Office Action mailed December 27, 2004, alleges that “[t]he specification discloses only tolerizing T cells to an antigen and not tolerizing a generic T-cell or tolerizing a T-cell in a graft or transplant recipient.”

Contrary to the Examiner’s above assertion, claims 64 and 65 do recite tolerizing T-Cells to an antigen. Claim 64 recites, in the preamble, “[a] method for preparing a dendritic cell capable of tolerizing a T-cell, said method comprising.” However, the preamble of claim 64 is further informed by the method step of “loading the dendritic cells with an antigen which is MHC-matched to a clonal T-cell, wherein the dendritic cells are capable of tolerizing the clonal T-cell in vitro to the antigen.” As such, by its own recited method steps, claim 64 describes tolerizing a T-cell to an antigen, which the Examiner has agreed has support in the specification.

Claim 65 recites, in the preamble, “[a] method for preparing a dendritic cell for tolerizing a T-cell in a graft or transplant recipient, said method comprising.” However, as in claim 64, the preamble of claim 65 is informed by the recited method step of “loading-said dendritic cells with an antigen against which said T-cell is to be tolerized.” Again, by its own recited method steps, claim 65 describes tolerizing a T-cell to an antigen, which the Examiner has agreed has support in the specification.

To the extent it may be relevant that the preamble recites the use of the claimed method in treating a graft or transplant recipient, support for such a use is found through out the specification. Specifically, the specification, at ¶¶ 7, 18, and 29 specifically notes the use of the invention in treating graft-versus-host and host-versus-graft disease. These diseases only arise in graft or transplant recipients. As such, the specification provides support for tolerizing a T-cell in a graft or transplant recipient.

Given that the objected to new matter appears only in the preambles and that the preambles of claims 64 and 65 are informed by recited method steps indicating the tolerization of a T-cell to an antigen, appellants respectfully submit that the specification provides adequate

written description for claims 64 and 65. Consequently, appellants respectfully request that the rejection of claims 64 and 65 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claims allowed.

The Order Of Steps In Claims 69 Through 81 Have Support In The Specification

As noted *supra*, the Examiner has rejected claims 69 through 81 as constituting new matter as there is allegedly “no support for the specific order of the steps in claim 69, *e.g.*, contacting the cells with antigen before contacting the DCs with Dex before activating the DCs. Nor does the specification support the specific order of the steps in claim 77, *e.g.*, contacting the cells with Dex before activating the DCs before contacting the DCs with antigen.” Office Action mailed July 26, 2005, at Page 8.

Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one. However, such a result can ensue when the method steps implicitly require that they be performed in the order written. *Interactive Gift Exp. Inc. v. Compuserve Inc.*, 257 F.3d 1323, 59 USPQ2d 1401 (Fed. Cir. 2001). There is a two-part test for determining if the steps of a method claim that do not otherwise recite an order must nonetheless be performed in the order in which they are written. First, the court looks to the claim language to determine if, as a matter of logic or grammar, they must be performed in the order written. *Altiris Inc. v. Symantec Corp.*, 318 F.3d 1363, 65 USPQ2d 1865 (Fed. Cir. 2003). If not, it next looks to the rest of the specification to determine whether it directly or implicitly requires such a narrow construction. *Id.*

Claims 69 and 77, from which claims 70-76 and 78-81 depend respectively, recite the transitional phrase “said method comprising.” As such, the preamble indicates that certain steps must be followed, but gives no logical or grammatical indication that the steps must be performed in a specific order. Further, the claim elements at issue do not grammatically refer to one another in such away so as to logically or grammatically indicate that they must be performed in the order written. The steps at issue of claim 69 recite:

contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced, thereby loading said dendritic cells with the antigen;
contacting said dendritic cells with dexamethasone;

activating the CD40 receptor on said dendritic cells.

None of these steps make any reference to one another in such a way to indicate logically or grammatically that anyone of the steps must take place before any other. Each step recites doing something to dendritic cells, and there is nothing to indicate in what order these steps have to be performed on the dendritic cells.

Similarly, the steps at issue in claim 77 recite:

contacting a dendritic cell with dexamethasone *in vitro*;
activating the dendritic cell through the CD40 receptor;
contacting the dendritic cell with an antigen, thereby loading the dendritic cell with the antigen.

As with claim 69, none of these steps make any reference to one another in such a way to indicate logically or grammatically that anyone of the steps must take place before any other. Each step recites doing something to dendritic cells, and there is nothing to indicate in what order these steps have to be performed on the dendritic cells.

As there is nothing logically or grammatically present in the claims indicating in what order the steps at issue should be pursued, we should next look to the rest of the specification to determine whether it directly or implicitly requires such a narrow construction. *Altiris Inc. v. Symantec Corp., surpa.*

As to claim 69, support exists in the specification for contacting the cells with antigen before contacting the DCs with Dex before activating the DCs. Specifically, ¶ 35 recites testing T-cells exposed to “p3-13-pulsed DEX-treated CD40-triggered DC.” This description of the DC follows exactly the listing of the elements at issue in claim 69. To wit: A) contacting cells with antigen relates to “p3-13 pulsed;” B) contacting the cells with Dex relates to “DEX-treated;” and C) activating the DCs relates to “CD40-triggered DC.” Thus, appellants respectfully submit that a dendritic cell described using the precise order of steps outlined in claim 69 is recited in the specification.

As to claim 77, support exists in the originally filed claims for contacting the cells with Dex before activating the DCs before contacting the DCs with antigen. To wit: originally filed claim 1 recites, in relevant part, “activating said dendritic cells in the presence of a glucocorticoid hormone; and loading said dendritic cells with an antigen against which said T-cell response is to

be reduced.” Further, original claim 13 recites:

A method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen, comprising:
providing said dendritic cell with a glucocorticoid hormone;
activating said dendritic cell; and
providing said dendritic cell with said antigen.

In comparison to claim 77, the same order of steps is recited. To wit: A) “providing said dendritic cell with a glucocorticoid hormone” relates to “contacting the cells with Dex;” B) “activating said dendritic cell” relates to “activating the DCs;” and C) “providing said dendritic cells with said antigen” relates to “contacting the DCs with an antigen.” As such, appellants respectfully submit that originally filed claim 13 specifically recites the same order of steps present in claim 77.

As the language of the claims does not logically or grammatically require the steps at issue to be performed in any specific order, and as the order of the steps in claims 69 and 77 are supported in the specification and originally filed claims, appellants respectfully submit that claims 69 and 77 do not introduce new matter. Consequently, appellants respectfully request that the rejection of claims 69 and 77 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claims allowed. Further, as claims 70-76 and 78-81 depend from claims 69 and 77 respectively, appellants respectfully request that these claims are allowable at least as depending from an allowable independent claim.

The “Peptide Antigen” Of Claims 43 and 75 Has Support In The Specification

As noted *supra*, the Examiner has rejected claims 43 and 75 as constituting new matter as allegedly “[t]he specification does not disclose peptide antigens and original claim 9 discloses only synthetic peptides.” Office Action mailed July 26, 2005, at Page 8.

Appellants respectfully submit that support for “peptide antigens” exists throughout the specification. Specifically, ¶ 19 of the specification indicates that “[a]n antigen is typically a peptide capable of binding to a major histocompatibility complex (MHC) I and/or II molecule.” Further, in the same paragraph, the specification goes on to relate that “[a]n antigen may also be a synthetic peptide,” clearly indicating that the previous use of the term “peptide” was meant to

include naturally occurring as well as synthetic peptides. In addition, Example 4 (¶ 35 of the specification) relates the use of hsp65 protein and the peptide epitope p3-13 as antigens. Both of these antigens constitute naturally occurring peptides. As such, appellants respectfully submit that support exists in the specification for the use of peptide antigens at least as the specification, reasonably read, indicates that both naturally occurring and synthetic peptide antigens may be part of the invention, and as one example of the specification uses naturally occurring peptides as antigens. Consequently, appellants respectfully request that the rejection of claims 43 and 75 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claims allowed.

The “Precursor Of A Dendritic Cell” Of Claim 53 Has Support In The Specification

As noted *supra*, the Examiner has rejected claim 53 as constituting new matter as allegedly “the specification does not disclose ‘a precursor of a DC.’” Office Action mailed July 26, 2005, at Page 8.

Appellants respectfully submit that support for “a precursor of a dendritic cell” exists throughout the specification. Specifically, ¶ 18 of the specification indicates that “culturing peripheral blood monocytes from the host to differentiate into dendritic cells.” As such, the specification, at ¶ 18, clearly indicates that the appellants were in possession of a precursor to dendritic cells, to wit: peripheral blood monocytes. Language identical to the above noted portion of ¶ 18 also appears at ¶¶ 19 and 20. In addition, ¶ 36 of the specification specifically outlines methodology that may be used to generate dendritic cells from their precursors, peripheral blood monocytes.

Furthermore, original claim 1 recites “culturing peripheral blood monocytes from said host to differentiate into dendritic cells.” As with the cited portions of the specification, original claim 1 clearly indicates that the appellants were in possession of a precursor to dendritic cells.

Further, original claim 29 recites:

The method according to claim 13, wherein providing said dendritic cell with a glucocorticoid hormone comprises providing a precursor of said dendritic cell with said glucocorticoid hormone in vitro.

As such, original claim 29 further indicates that the appellants were in possession of a precursor of a dendritic cell.

In light of the discussion *supra*, appellants respectfully submit support exists in the specification for “precursors of dendritic cell” at least as the specification, indicates that the appellants were in possession of a precursor of dendritic cells and methods to generate dendritic cells from this precursor. Further, original claim 29 clearly indicates that the appellants were *ipsis verbis* in possession of a precursor of a dendritic cell. Consequently, appellants respectfully request that the rejection of claim 53 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claim allowed.

The “Antigen Defined By The Response Of A T-Cell” Of Claim 58 Has Support In The Specification

As noted *supra*, the Examiner has rejected claim 58 as constituting new matter as allegedly “the specification does not disclose ‘an antigen defined by the response of a T-cell.’” Office Action mailed July 26, 2005, at Page 8.

Appellants respectfully submit that support for an “antigen defined by the response of a T-cell” exists throughout the specification. Specifically, ¶ 22 of the specification notes that “the invention provides a method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen comprising . . . providing the dendritic cell with the antigen.” As is well known in the art, T-cells have individually variable receptors, directly analogous to the antibodies, that give a particular T-cell a unique ability to detect particular antigens presented by antigen presenting cells. *See, e.g.*, Benjamin Lewin, Genes V, 1103-1108 (1994). As a particular T-cell will only responds to particular antigens, it is implicitly and inherently described in ¶ 22 of the specification that once the T-cell response to be tolerized is identified, the proper antigen to tolerize it can be selected. Thus, implicit and inherent written description for “an antigen defined by the response of a T-cell” exists in the specification.

Further, ¶ 7 of the specification indicates that “the present invention, therefore, indicates that such DC loaded with appropriate antigens can be exploited as a novel approach for specifically down regulating unwanted T-cell responses in vivo.” As above, this statement of the specification provides implicit an inherent support for “an antigen defined by the response of a T-

cell.” Specifically, the appropriate antigens are selected based on the unwanted T-cell response. In this manner, the appropriate antigens are defined by the unwanted response of a T-cell.

As such, appellants respectfully submit that adequate written description exists in the specification for the phrase “an antigen defined by the response of a T-cell” as recited in claim 58. Consequently, appellants respectfully request that the rejection of claim 58 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claim allowed.

The “DCs Derived From A Graft Or Transplant Donor” Of Claims 61, 65, 68, 78, 80, And 81 Has Support In The Specification

As noted *supra*, the Examiner has rejected claims 61, 65, 68, 78, 80, and 81 as constituting new matter as allegedly “the specification does not disclose ‘DCs derived from a graft or transplant donor.’” Office Action mailed July 26, 2005, at Page 9.

To comply with the written description require of 35 U.S.C. § 112, first paragraph, each claim limitation must be expressly, implicitly, or inherently support in the originally filed disclosures. MPEP § 2163(II)(A)(3)(b). Further, the subject matter of the claim need not be described literally, *in haec verba*, in order for the disclosure to comply with the written description requirement. MPEP § 2163.02.

Appellants respectfully submit that support for “DCs derived from a graft or transplant donor” exists throughout the specification. Specifically, ¶ 28 of the specification provides that

The invention also provides a method for the treatment of an individual suffering from, or at risk of suffering from, a disease associated with at least part of the immune system of the individual , including providing the individual with a dendritic cell and/or a functionally modified T-cell . Preferably, the dendritic cell and/or the functionally modified T-cell or precursors thereof are derived from an HLA-matched donor. Preferably, the HLA-matched donor is the individual.

This paragraph of the specification implicitly and inherently provides that the dendritic cells may be obtained from a graft or transplant donor. The paragraph cited indicates that it is preferable that the dendritic cells to be modified come from the individual to be treated, but in so stating implicitly and inherently supports the notion that dendritic cells may come from other sources, such are a donor of a graft or transplant. Further, the cited paragraph indicates that it is preferable that the dendritic cells are derived from an HLA-matched donor. As donors of

transplants and grafts will very typically be HLA-matched to the recipient to aid in avoiding rejection, such a statement implicitly and inherently supports the notion that dendritic cells may come from the donor of a graft or transplant. Consequently, appellants respectfully request that the rejection of claims 61, 65, 68, 78, 80, and 81 under 35 U.S.C., first paragraph, as constituting new matter be withdrawn and the claims allowed.

(iii) 35 U.S.C. § 112, first paragraph, lack of enablement

Claims 1 and 40-81 stand rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner in the Office Action mailed Jun 29, 2001, at Page 4, asserts that

The specification, while being enabling for the in vitro induction of non-responsiveness of MHC matched clonal T-cells to a defined antigen when dexamethasone-treated dendritic cells have been loaded with the same defined antigen does not reasonably provide enablement for in vivo or in vitro induction of non-responsiveness of polyclonal T cells to any undefined antigen or the in vivo induction of non-responsiveness when an “un-wanted T cell response” is ongoing.

In response to the appellants arguments, the Examiner further alleges, in the Office Action mailed September 19, 2002, at pages 2 and 3, that

It appears then that the applicant is arguing that the invention of the instant claims function through a previously undescribed mechanism. Said mechanism would then be considered unexpected and accordingly, unpredictable. Given the unpredictability of the invention of the instant claims, some sort of enablement, in addition to mere assertion would be required.

In the Office Action mailed May 21, 2003, the Examiner, at page 3, indicates that:

The rejection is based on two key factors. First the specification fails to disclose precisely how the antigens that induce unwanted T cell responses are established. Second, given that the claims are drawn to a method for preparing a pharmaceutical composition, the specification fails to adequately disclose that the DCs would function as a pharmaceutical composition *in vivo*.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *In re Buchner* 929 F.2d 660, 662, 18 USPQ2d 1331, 1332 (Fed. Cir.

1991). Further, a patent need not teach, and preferably omits, what is well known in the art. *Id.* To comply with the enablement requirement, it is not necessary to enable one of ordinary skill in the art to make a use a perfected commercially viable embodiment of absent a claim limitation to that effect. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.2d 1333, 1338, 68 USPQ2d 1940, 1044 (Fed. Cir. 2003). Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those of skill in the art to make and use the invention. MPEP § 2164. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. *In re Fisher*, 4127 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Appellants respectfully submit that the specification, along with the Declaration of Rienk Offrenga, and the level of knowledge and skill in the art, provide enabling support for claims 1 and 40-81. Appellants will first address the Examiner's assertion that when a previously undescribed mechanism of action is unexpected it is therefore unpredictable for the purposes of enablement. *See*, Office Action mailed September 19, 2002, at pages 2 and 3; Office Action mailed May 21, 2003, at Page 3. Appellants respectfully submit that an unexpected result in not necessarily unpredictable for the purposes of enablement. If the Examiner's assertion were valid, any argument for nonobviousness citing unexpected results (as is permissible under MPEP § 716.02) would automatically lead to a rejection for lack of enablement under 35 U.S.C. § 112, first paragraph. Appellants respectfully submit that the established value of unexpected results in demonstrating nonobviousness would be seriously undermined if any demonstration of unexpected results automatically indicated a finding of unpredictability.

Further, an unexpected result does not necessarily equate to an unpredictable result. If the odds of a particular result occurring are very low, then the occurrence of that result may be unexpected, but it is not unpredictable. In addition, the appellants, persons of knowledge and skill in the art, would not have engaged in the experimentation necessary to demonstrate the unexpected result if they did not first predict the result would occur. Last, once the unexpected results of the invention are described, the results are no longer unpredictable as one could follow the teachings of the specification and arrive at similar results. As such, appellants respectfully submit, contrary to the Examiner's assertion, that the unexpected results that the give rise to the present invention do not make the present invention unpredictable in terms of enablement.

Appellants further respectfully submit, as to the Examiners first key factor of the rejection, that the specification adequately enables how the antigens that induce unwanted T cell responses are established. Appellants respectfully submit that which antigen a T-cell response is to be reduced (an "unwanted T-cell response") is subjective in nature. The selection of the antigen to which a T-cell response is to be reduced is a decision left to the practitioner of the invention (presumably one of knowledge and skill in the art) and any antigen can be selected (using the knowledge and skill in the art) for use in practicing the present invention. Further, the appellants provide two examples of antigens which were tested to see if a T-cell response to them was reduced. Specifically, Example 4 of the specification (§ 35) shows the reduction of a T-cell response to the antigens hsp65 protein and p3-13. For the purposes of testing the invention, the T-cell response to hsp65 and p3-13 were "unwanted" as the practitioners of the invention wished to reduce the T-cell response to these antigens. As such, the selection of the "unwanted T-cell response" and the corresponding antigen(s) which induces that T-cell response is placed in the hands of one of skill in and knowledge in the art using selection criteria based on that skill and knowledge. As such, the selection of an "unwanted T-cell response" according to the present invention can be arrived at by one of skill in the art and thus allows one of skill and knowledge to make and use the claimed invention.

In addition, an advantage of the invention is that the exact identity of all possible antigens is not required. Therefore, the invention is not limited to the use of any specific antigen. A person of ordinary skill in the art would recognize that professional antigen presenting cells (APCs)¹, such as dendritic cells, can be loaded with any antigen for which tolerization is desired (*i.e.*, the unwanted immune response). Antigens will be taken up, processed and displayed by MHC class I and II molecules on the surface of the APC to surrounding T-cells (Kampgen *et al.* (1991), Class II Major Histocompatibility Complex Molecules of Murine Dendritic Cells: Synthesis, Sialylation of Invariant Chain, and Antigen Processing Capacity are Down-Regulated Upon Culture. *Proc. Natl. Acad. Sci. U S A.* 88(8):3014-3018 (discussing the abundant antigen

¹ Antigen presenting cells (APC) are cells derived from bone marrow and comprise a heterogeneous set of cells, including dendritic cells in lymphoid organs, Langerhans cells in skin, and certain types of macrophages, which present antigens on MHC glycoproteins. BRUCE ALBERTS *ET AL.*, MOLECULAR BIOLOGY OF THE CELL (2nd ed. Garland Publishing, Inc., 1989) pp. 1044-1057, 1045.

presentation by dendritic cells through MHC molecules)).² Thus, loading of an antigen may be accomplished by bringing dendritic cells into contact with any antigen source for which tolerization is desired, ranging from its own internal proteins (as in Figure 5 of the Declaration; Hancock *et al.*, 1996; and Kampgen *et al.*, 1991) or external sources, such as, purified peptides, proteins or cell extracts from grafts/transplants (for example, as in ¶¶ 35 and 43 of the specification). In Example 5 of the Declaration, the dendritic cells are syngeneic (*i.e.*, of the exact same origin and genetic make-up as the graft cells), hence expressing, or loaded with, antigens identical to the graft/transplant antigens.

Furthermore, antigens for specific diseases are known in the art. For example, multiple sclerosis is a demyelination disease, associated with an autoimmune response to the myelin basic protein. Nicholson *et al.* disclose alterations of an antigen and states that "[m]uch of the experimental work in models of autoimmunity has focused on the immune response to specific peptide ligands (cognate ligands)."³ In addition, Greten *et al.* disclose that "many HLA-A2-restricted antigens have been identified for human ... autoimmune diseases, and cancer."⁴ Finally, Stemme *et al.* disclose autoantigens derived from oxLDL as being of potentially "significant pathogenetic importance in atherosclerosis."⁵ Thus, the selection of an antigen for a specific disease is known in the art.

As explained herein, a limiting list of specific antigens is not expressly provided in the disclosure, as the invention is not limited to any specific antigen. In practice, when tolerizing a subject for grafts or transplants it is not even feasible to point out a single specific antigen, as there are typically many reactive antigens. As exemplified in the Declaration, for example, Figure 5, an entire spectrum of antigens derived from a graft/transplant can be displayed on alternatively activated dendritic cells according to the current invention. There simply is no need, nor is it desirable, to select a single antigen in order to reduce an unwanted immune

² Kampgen *et al.*, like Cronstein *et al.*, does not specifically list all possible antigens present in a cell.

³ Nicholson *et al.* (1998) Heteroclitic Proliferative Responses and Changes in Cytokine Profile Induced by Altered Peptides: Implications for Autoimmunity *Proc. Natl. Acad. Sci. U.S.A.* 95:264-269, 264.

⁴ Greten *et al.*, (1998) Direct Visualization of Antigen-specific T Cells: HTLV-1 Tax11-19-specific CD8⁺ T Cells are Activated in Peripheral Blood and Accumulate in Cerebrospinal Fluid From HAM/TSP Patients, *Proc. Natl. Acad. Sci. U.S.A.* 95:7568-7573, 7572.

⁵ Stemme *et al.* (1995) T Lymphocytes from human Atherosclerosis Plaques Recognize Oxidized Low Density Lipoprotein, *Proc. Natl. Acad. Sci. U.S.A.* 92:3893-3897, 3897.

response. Further, the antigens will depend on the genetic make-up of the host (HLA type). Thus, the specification provides the only possible enabling description of the antigens (for example, ¶ 7 of the specification, indicating "that such DC [dendritic cells] loaded with appropriate antigens [as can be selected by one of skill and knowledge in the art] can be exploited as a novel approach for specifically down regulating unwanted T-cell responses *in vivo*." (emphasis added). Further, specific antigens, be they multiple antigens from an allogeneic graft or transplant or specific antigens such as the myelin basic protein, are known in the art.

In addition, the Declaration under 37 C.F.R. § 1.132 states that "[t]he enclosed summary of the tests as set forth below also demonstrate the practical use of alternatively activated DC for modulation of the alloimmune response and show that these can induce a prolonged skin graft survival even in a complete MHC incompatible donor-recipient combination; and that Example 1 herein was based on Example 4 of the patent application" (page 2 of the Declaration). Further, a person of ordinary skill in the art knows that "[e]ach ... [animal] has a group of genes (the major histocompatibility complex or MHC) which codes for many proteins important for immune function. Among these are a group of proteins located on the plasma membranes of all nucleated cells in an individual's body called human leukocyte associated antigens (HLA antigens) Since no two persons (other than identical twins [and inbred laboratory strains, e.g., inbred mice]) have the same MHC genes, no two persons have the same HLA antigens" (ARTHUR J. VANDER, M.D. ET. AL., HUMAN PHYSIOLOGY: THE MECHANISMS OF BODY FUNCTION 621 (Mary Jane Martin and Susan Hazlett eds., McGraw-Hill Book Co. 4th ed. 1985) (emphasis in original) (*see also*, ABUL K. ABBAS, M.B.B.S., ET. AL., CELLULAR AND MOLECULAR IMMUNOLOGY 319 (W. B. Saunders Co., 1991) (both cited in an IDS submitted April 27, 2005, and not considered as the citation lacked the city of publication). Moreover, a person of ordinary skill in the art knows that "[t]he cell-mediated immune system is also mainly responsible for the recognition and destruction, *i.e.*, rejection, of tissue transplants [and that] on the surfaces of all nucleated cells of an individual's body are genetically determined antigenic protein molecules known as HLA or histocompatibility antigens. When tissue is transplanted from one individual to another, those surface antigens which differ from the recipient's are recognized as foreign and are destroyed by sensitized cytotoxic T cells" (*Id.* A. J. VANDER at 626, A. K. ABBAS at 319-320) (emphasis in

original). Hence, a person of ordinary skill in the art recognizes that the mice used as the donor and recipient have different HLA antigens, *see*, for example, the Declaration at page 5, which indicates the different HLA types for the mice, and that the surface antigens of the graft, which differ from the recipient's, will be recognized as foreign and be destroyed by the host T cells (*see also*, Hancock *et al.*, 1996, indicating the HLA types for the mice used and presuming that the reader is familiar with the basic concepts of allogenic rejection). Therefore, the "presumptions" of the authors are more "more than an attorney's assertion" (Office Action mailed December 27, 2004, at Page 3) and the inventor's § 1.132 Declaration does address the invention of the instant claims. More specifically, the inventor's Declaration addresses a method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host [allogenic graft rejection], said method comprising ... activating said dendritic cells with a means for reducing IL-12p40 production by said dendritic cells (or activating said dendritic cells with a glucocorticoid capable of activating a glucocorticoid receptor) [activating the dendritic cells with dexamethasone]; loading said dendritic cells with (or bringing said dendritic cells into contact with) an antigen against which said T-cell response is to be reduced; and forming a pharmaceutical composition comprising said loaded, activated dendritic cells for administration to the host, as recited in the pending claims (*e.g.*, claims 1 and 40).

The appellants have also provided evidence that the DCs in the example provide the same antigens as the skin graft cells and that an antigen-specific unwanted T cell response [allogenic graft rejection] is reduced (Office Action mailed December 27, 2004, at Page 3). For example, the Declaration states that "prolonged skin graft survival after treatment with alternatively activated H-2^b DC [indicating the HLA type] was **specific** for the H-2^b alloantigens as mice injected with DEX-LPS DC rejected skin grafts from DBA/1 mice (H-2^q) [HLA type different from the antigens loaded on the dendritic cells] in the same time ... as control mice" (page 10 of the Declaration) (emphasis added). Therefore, the Declaration does provide evidence that the DCs provide the same antigens as the skin graft cells, and that the unwanted T cell response, *e.g.*, graft rejection, is reduced.

The Examiner also asserts that the examples of the Declaration are not antigen specific – alloimmune responses are not considered to be antigen-specific responses. Office Action mailed December 27, 2004, at Page 3 The appellants respectfully disagree. As discussed herein, the

dendritic cells (DC) were specific for the H-2^b alloantigens, thus, the response is specific to the antigens of the graft cells.

The Examiner further asserts that appellants' argument "that professional antigen presenting cells (APCs)⁶, such as dendritic cells, can be loaded with any antigen for which tolerization is desired Thus, loading of an antigen may be accomplished by bringing dendritic cells into contact with any antigen source for which tolerization is desired, ranging from its own internal proteins (as in Figure 5 of the Declaration; Hancock *et al.*, 1996; and Kampgen *et al.*, 1991) or external sources, such as, purified peptides, proteins or cell extracts from grafts/transplants (for example, as in ¶¶ 35 and 43 of the specification)" (*see*, page 14 of the reply mailed November 21, 2003) is confusing, since it is unclear how DC can be loaded with any antigen ... if the identity of the said antigens has not been established" (Office Action mailed December 27, 2004, at pages 3-4). Appellants respectfully submit that a person of ordinary skill in the art clearly understands how dendritic cells can be loaded with antigens without having to determine the identity of each antigen (*see*, A. K. ABBAS at 319-320).

Moreover, the Examiner has provided no evidence to contradict the Offrenga Declaration. The Federal Circuit, in *In re Zurko*, states that the Board must make its findings based upon the written record. 59 USPQ2d 1693, 1997 (Fed. Cir. 2001). Here, the written record consists of the Offrenga Declaration and its cited art. The Examiner has produced nothing other than his own understand and experience to refute appellants evidence. Accordingly, appellants respectfully request that the Offrenga Declaration be accepted as proof that the transplant models described in the Declaration establish how an unwanted T-cell response can be selected.

Hence, a person of ordinary skill in the art knows "how dendritic cells can be loaded with any antigen for which tolerization is desired if the identity of said antigens has not been established" (Office Action mailed December 27, 2004, at Page 4).

In addition, the Examiner further asserts that the appellants' statement that antigens for specific diseases are known in the art is a "severe oversimplification" (Office Action mailed December 27, 2004, at Page 4) and that Greten *et al.*, Stemme *et al.* and Nicholson *et al.* do not provide any definitive statements regarding T cells specific for the described antigens being

⁶ See footnote 1, *supra*

absolutely known to be pathogenic (*Id.*). The appellants respectfully disagree. For example, Greten *et al.* at 7568 state "[i]t has been previously demonstrated that circulating CD8⁺ cytotoxic T lymphocytes (CTLs) in patients with HAM/TSP react against HTLV-1 protein products, and an immunodominant HLA-A2-restricted epitope (HTLV-1 Tax11-19)," and Stemme *et al.* at 3896 state that their work "strongly suggests that the T-cell response was mounted against an HLA-DR-restricted, processed antigen derived from ox-LDL." The Office then goes on to discuss clinical difficulties encountered in the treatment of multiple sclerosis by reducing the number of T cells specific for the known antigen, myelin basic protein (MBP). Hence, the Office acknowledges that MBP is a known antigen for multiple sclerosis. Regardless of whether or not the authors "tortured" their analysis of the data (page 4 of the Office Action), the antigen is known in the art (*see*, Zhang *et al.* at 212).

In view of the foregoing, appellants respectfully submit that the selection of an "unwanted T-cell response" according to the present invention can be arrived at by one of skill in the art and thus allows one of skill and knowledge to make and use the claimed invention.

In regards to the Examiners second key factor, the Examiner states that the specification "does not reasonably provide enablement for, *in vivo* or *in vitro* induction of non-responsiveness of polyclonal T cells to any undefined antigen or the *in vivo* induction of non-responsiveness when an 'unwanted T-cell response' is ongoing" (emphasis added; Office Action mailed May 21, 2003, at Page 3). The appellants respectfully submit that the Examiner appears to indirectly put forward the position that the *in vitro* data of the specification does not support claims to *in vivo* uses.⁷ The appellants have described how the invention functions using *in vitro* working examples. However, the Examiner acknowledges enablement of only *in vitro* use of the invention. The appellants respectfully submit that the specification is enabling for both *in vitro* and *in vivo* induction of non-responsiveness of polyclonal T cells.⁸ As the Office bears the

⁷ The appellants submit that a requirement for *in vivo* data to support *in vivo* use is contrary to established law (*see* MPEP § 2164.02, citing *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565-1566, 39 USPQ2d (BNA) 1895 (Fed. Cir. 1996)).

⁸ The Office Actions, while rejecting the claims for an alleged lack of written description seem to the appellants to be directed to enablement of glucocorticoids other than dexamethasone. Cronstein *et al.*, (1992) A Mechanism for the Antiinflammatory Effects of Corticosteroids: The Glucocorticoid Receptor Regulates Leukocyte Adhesion to Endothelial Cells and Expression of Endothelial-leukocyte Adhesion Molecule 1 and Intercellular Adhesion Molecule 1, *Proc. Nat. Acad. Sci. U.S.A.* 89:9991-9995) (of record in the case) shows the use of dexamethasone and

burden of presenting reasons for the lack of an enabling correlation between *in vitro* and *in vivo* results, in the absence of any such reasoning, the appellants assume that no challenge to the correlation of the *in vitro* data to use *in vivo* is intended. Thus, the appellants submit that the *in vitro* data provided in the specification supports and enables *in vivo* use of the claimed compositions. Furthermore, the appellants respectfully submit that the *in vitro/in vivo* correlation is firmly established by the executed Declaration, submitted herewith.

In addition, the appellants submit that the Examiner's second key factor is answered in the Declaration. The examples provided in the Declaration demonstrate unequivocally the use of the alternatively stimulated dendritic cells as a pharmaceutical composition *in vivo* (Office Action mailed May 21, 2003, at Page 3). The alternatively activated dendritic cells are capable of inducing a prolonged skin graft survival when administered as a pharmaceutical composition *in vivo* to mice having undergone a skin graft with an incompatible donor-recipient combination.

Figures 5a and 5b of the Declaration show a striking difference in skin graft survival. In Figure 5a the administered dendritic cells are of the same type C57BL/6 (H-2^b) as the graft (*i.e.*, carrying and displaying the same antigens), demonstrating that alternatively activated dendritic cells displaying antigens identical to the antigens displayed on the graft cells are capable of tolerizing a subject and result in prolonged (about doubled) graft survival. The Examiner alleges that no antigen loaded DCs were used in the disclosed experiments. The appellants would again like to stress that the activated antigen presenting dendritic cells in this experiment do display antigens. In particular, the dendritic cells present the same antigens as the skin graft cells, which are also of C57BL/6 (H-2^b) origin, thereby inducing tolerization to these antigens (*see also*, Hancock *et al.*, 1996). The recipient/host mice are of a different type, BALB/c (H-2^d), than the donor and therefore will normally immunologically react to the allogeneic C57BL/6 graft. *Id.* Thus, dendritic cells loaded with C57BL/6, type H-2^b, antigens, function as a pharmaceutical

references comparison to the weaker glucocorticoid, cortisol, as an example of glucocorticoids. The authors of this paper conclude that "antagonism by dexamethasone ... is a specific instance of the general biological principle that the glucocorticoid receptor is a hormone-dependent regulator of transcription" (Cronstein *et al.*, summary). Cronstein *et al.* recognize that the results that they obtained with the example dexamethasone are applicable to the entire glucocorticoid class. Likewise, the appellants used dexamethasone as a representative of all glucocorticoids and apply those results to glucocorticoids in general. In the absence of reasoning why results obtained with dexamethasone would not be applicable to glucocorticoids in general, the appellants submit that the data enables all glucocorticoids and that the express word "glucocorticoids" provides adequate written description of

composition *in vivo*, as described in the specification, and the specification teaches a person of ordinary skill in the art how the antigens that induce unwanted T cell responses are established (e.g., graft derived).

In Figure 5b, a different skin graft was used (DBA/1 (H-2^a) origin). Indeed, here the C57BL/6-antigen displaying C57BL/6 dendritic cells (the graft and dendritic cells are not syngeneic) were ineffective in prolonging the survival of the DBA/1 graft (i.e., no tolerization of the graft was observed). Thus, Figure 5a illustrates the effectiveness of the claimed method and *in vivo* function of the invention, as described in the specification, confirming the *in vivo* applicability of the appellants' *in vitro* tests (for example, Example 4). Figure 5b illustrates the specificity of the claimed method.

The Office asserts that no antigen-loaded DCs were used in the disclosed experiments [of the Declaration]. Hancock *et al.* (1996), Costimulatory function and expression of CD40 ligand, CD80, and CD86 in vascularized murine cardiac allograft rejection., *Proc. Natl. Acad. Sci. U S A.* 93(24):13967-13972, describes graft versus host rejection with C57BL/6 (H-2b) and BALB/c (H-2d) mice through CD40L binding. As will be noted by review of Hancock *et al.*, the authors of the reference do not list the source or identity of all of the antigens, other than by reference to the particular mice (for example, C57BL/6 (H-2^b) and BALB/c (H-2^d), page 13967, second column), but simply refer to allograft rejection (for example, Figures 1-3 and Table 2). Thus, Hancock *et al.* presumes that a person of ordinary skill in the art would recognize the source of the antigens (the allogeneic mice). Likewise, the Declaration does not expressly state the source of the antigens. The source of the antigens is presented in the form of a description of the allogeneic mice C57BL/6 (H-2^b) and BALB/c (H-2^d).

Moreover, the Examiner has provided no evidence to contradict the Offrenga Declaration. The Federal Circuit, in *In re Zurko*, states that the Board must make its findings based upon the written record. 59 USPQ2d 1693, 1997 (Fed. Cir. 2001). Here, the written record consists of the Offrenga Declaration and its cited art. The Examiner has produced nothing other than his own understand and experience to refute appellants evidence. Accordingly, appellants respectfully request that the Offrenga Declaration be accepted as proof that the transplant models described in

"glucocorticoids."

the Declaration establishes how the *in vitro* experimentation outlined in the specification is directly applicable to *in vivo* results.

Last, the Examiner asserts, in the Office Action mailed July 26, 2005, at Page 5, that no nexus has been established between a reduction in IL12p40 production and a reduction in an unwanted T cell response. Further, the Examiner asserts “as no cause an effect has been tested for, and thus, not established, it is just as, or more, likely that the reduction of IL12p40 is just an artifact, or at most a marker for the reduction of an antigen specific T cell response.” *Id.*

Appellants respectfully submit that the nexus between IL12p40 production and a reduction in unwanted T cell response exists in the specification. Specifically, Example 3 (¶ 34) indicates that a Key feature of CD40 triggered DC for initiating T-cell immunity resides in their ability to produce the proinflammatory cytokine IL-12. The specification therein cites the work of Cella *et al.*, J Exp Med 184: 747, 1996, Koch *et al.*, J Exp Med 184: 741, 1996, and de Saint Vis *et al.*, J Immunol 160: 1666, 1998 as support for this statement. Further, when the findings of Example 3 are combined with those of Example 4, it would be apparent to one of skill in the art that the corresponding reduction of IL12p40 production in Example 3 leads to the reduction of a T-cell response presented in Example 4. As such, appellants respectfully submit that one of skill in the art would agree that a nexus exists between IL12p40 production and a reduction in unwanted T cell response.

Further, an inventor need not comprehend the scientific principles upon which the practical effectiveness of the invention rests. *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 219 USPQ 1137 (Fed. Cir. 1983). As such, even if, as asserted by the Examiner, the reduction of IL12p40 is just a marker for the reduction of an antigen specific T cell response, appellants need not understand exactly how the invention works. It is sufficient that the invention does work and that the specification, in combination with the knowledge and skill in the art, allows one to make and use the invention.

In view of the foregoing, appellants respectfully submit that the specification does disclose, in the only feasible way, precisely how the antigens that induce unwanted T cell responses are established. In addition, the specification describes a mechanism of the invention using *in vitro* data which correlates and enables use *in vivo*. Thus, a person of ordinary skill in the art, who would recognize the source of the antigens from the description in the specification,

is enabled to practice the invention *in vitro* and *in vivo*. Therefore, as one of skill in the art, using the knowledge and skill in the art, can practice the present invention, including the selection of an "unwanted T-cell response," appellants respectfully submit that claims 1, and 40-81 are enabled under 35 U.S.C. § 112, first paragraph. See, *In re Fisher*, 4127 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Consequently, appellants respectfully request that the rejections of claims 1 and 40-81 under 35 U.S.C., first paragraph, for lack of enablement be withdrawn and the claims allowed.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Dan J. Morath", with a long horizontal flourish extending to the right.

Daniel J. Morath, Ph.D.
Registration No. 55,896
Attorney for Applicant(s)
TRASKBRITT
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

Date: January 5, 2006

DJM/djm

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(8) CLAIMS APPENDIX

1. A method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host, said method comprising:

culturing peripheral blood monocytes from said host to differentiate into dendritic cells;
activating said dendritic cells with a means for reducing IL-12p40 production by said dendritic cells;

loading said dendritic cells with an antigen against which said T-cell response is to be reduced; and

forming a pharmaceutical composition comprising said loaded, activated dendritic cells for administration to said host.

40. A method for preparing a pharmaceutical composition for reducing an unwanted T-cell response in a host against an antigen, said method comprising:

culturing peripheral blood monocytes from said host to differentiate into dendritic cells;
activating said dendritic cells with a glucocorticoid capable of activating a glucocorticoid receptor;

bringing said dendritic cells into contact with an antigen against which said T-cell response is to be reduced; and

forming a pharmaceutical composition comprising said loaded, activated dendritic cells.

41. The method according to claim 40, further comprising activating a CD40 receptor on said dendritic cells.

42. The method according to claim 41, wherein activating the CD40 receptor comprises incubating the dendritic cells with a substance selected from the group consisting of a CD8-40L fusion protein, a trimeric form of CD40L consisting of CD40L molecules to which a modified leucine zipper has been attached, anti-CD40 antibodies, and cells that express CD40L.

43. The method according to claim 40, wherein bringing said dendritic cells into contact with an antigen comprises incubating said dendritic cells with at least one peptide representing at least one antigen of interest before activating said dendritic cells with said substance capable of activating the glucocorticoid receptor.

44. The method according to claim 40, wherein bringing said dendritic cells into contact with an antigen comprises incubating said dendritic cells with cells containing at least one antigen of interest before activating said dendritic cells with said substance capable of activating the glucocorticoid receptor .

45. The method according to claim 40, wherein bringing said dendritic cells into contact with an antigen against which said T-cell response is to be reduced comprises loading said dendritic cells with at least one synthetic peptide representing at least one antigen of interest after activating said dendritic cells with said substance capable of activating the glucocorticoid receptor .

46. The method according to claim 40, wherein activating said dendritic cells with said substance capable of activating the glucocorticoid receptor comprises activating said dendritic cells such that said dendritic cells secrete interleukin-10.

47. The method according to claim 40, wherein said T-cell is a T-helper cell.

48. The method according to claim 40, wherein bringing said dendritic cells into contact with an antigen comprises incubating said dendritic cells with a cell homogenate containing at least one antigen of interest before activating said dendritic cells with said substance capable of activating the glucocorticoid receptor.

49. The method of claim 40, further comprising incubating the dendritic cells with a substance selected from the group consisting of lipopolysaccharide (LPS) and poly/I/C.

50. The method of claim 40, wherein said glucocorticoid capable of activating the glucocorticoid receptor comprises dexamethasone.

51. A method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen, comprising:

providing said dendritic cell with a substance capable of activating a glucocorticoid receptor;

activating said dendritic cell; and

providing said dendritic cell with said antigen, wherein said dendritic cell is capable of tolerizing a T-cell for said antigen.

52. The method according to claim 51, wherein providing said dendritic cell with the substance capable of activating a glucocorticoid receptor is in vitro.

53. The method according to claim 51, wherein providing said dendritic cell with said substance capable of activating the glucocorticoid receptor comprises providing a precursor of said dendritic cell with said substance capable of activating the glucocorticoid receptor in vitro.

54. The method according to claim 51, wherein said-substance capable of activating the glucocorticoid receptor comprises dexamethasone.

55. The method according to claim 52, wherein said substance capable of activating the glucocorticoid receptor enhances secretion of IL-10 by said dendritic cells.

56. A method for preparing an isolated dendritic cell, said method comprising:
isolating peripheral blood monocytes from a subject;
culturing the peripheral blood monocytes to differentiate into dendritic cells;
activating the dendritic cells with a glucocorticoid;
loading the dendritic cells with an antigen; and

isolating said loaded, activated dendritic cells.

57. The method according to claim 56, wherein the glucocorticoid is dexamethasone.

58. The method according to claim 56, wherein loading said dendritic cells with an antigen comprises loading said dendritic cells with an antigen defined by a response of a T-cell.

59. The method according to claim 56, wherein the antigen comprises an allogeneic antigen.

60. The method according to claim 59, wherein the glucocorticoid is dexamethasone.

61. The method according to claim 60, wherein loading said dendritic cells with an antigen comprises contacting said dendritic cells with cells derived from a graft or transplant donor.

62. The method according to claim 61, wherein the dendritic cells are derived from the graft or transplant recipient.

63. The method according to claim 56, further comprising incubating the dendritic cells with a substance selected from a group consisting of a CD8-40L fusion protein, a trimeric form of CD40L consisting of CD40L molecules to which a modified leucine zipper has been attached, anti-CD40 antibodies, and cells that express CD40L.

64. A method for preparing a dendritic cell capable of tolerizing a T-cell, said method comprising:

- culturing peripheral blood monocytes to differentiate into dendritic cells;
- activating the dendritic cells with dexamethasone; and
- loading the dendritic cells with an antigen which is MHC-matched to a clonal T-cell, wherein the dendritic cells are capable of tolerizing the clonal T-cell in vitro to the antigen.

65. A method for preparing a dendritic cell for tolerizing a T-cell in a graft or transplant recipient, said method comprising:

- culturing peripheral blood monocytes from said graft or transplant recipient to differentiate into dendritic cells;
- activating said dendritic cells; and
- loading-said dendritic cells with an antigen against which said T-cell is to be tolerized.

66. The method according to claim 65, wherein activating said dendritic cells comprises administering a glucocorticoid.

67. The method according to claim 66, wherein activating said dendritic cells comprises administering dexamethasone.

68. The method according to claim 65, wherein loading said dendritic cells with an antigen comprises contacting said dendritic cells with cells derived from a graft or transplant donor.

69. A method for preparing a pharmaceutical composition for reducing an unwanted T-cell response to an antigen in a host, said method comprising:

culturing peripheral blood monocytes from said host to differentiate into dendritic cells *in vitro*;

contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced, thereby loading said dendritic cells with the antigen;

contacting said dendritic cells with dexamethasone;

activating the CD40 receptor on said dendritic cells; and

forming a pharmaceutical composition comprising said loaded, activated dendritic cells.

70. The method according to claim 69, wherein activating the CD40 receptor comprises culturing the dendritic cells with a substance selected from the group consisting of a CD8-40L fusion protein, a trimeric form of CD40L comprising CD40L molecules having a modified leucine zipper covalently attached to said CD40L molecules, anti-CD40 antibody, and cells that express CD40L.

71. The method according to claim 69 further comprising contacting the dendritic cells with lipopolysaccharide (LPS) or polyI/C.

72. The method according to claim 69, comprising contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced before contacting said dendritic cells with dexamethasone.

73. The method according to claim 72, wherein contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced comprises co-culturing said dendritic cells and cells containing at least one antigen of interest.

74. The method according to claim 69, comprising contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced after contacting said dendritic cells with dexamethasone.

75. The method according to claim 74, wherein contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced comprises contacting said dendritic cells with at least one isolated peptide having at least one antigenic region of interest.

76. The method according to claim 72, wherein contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced comprises contacting said dendritic cells with a cell homogenate containing at least one antigen of interest.

77. A method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen, the method comprising:

contacting a dendritic cell with dexamethasone *in vitro*;
activating the dendritic cell through the CD40 receptor; and
contacting the dendritic cell with an antigen, thereby loading the dendritic cell with the antigen, and forming a dendritic cell capable of tolerizing a T-cell for the antigen.

78. The method according to claim 77, wherein the dendritic cell is derived from a graft or transplant donor.

79. The method according to claim 77, further comprising:
isolating peripheral blood monocytes from a subject;
culturing the peripheral blood monocytes to differentiate into dendritic cells;
incubating the dendritic cells with a substance selected from the group consisting of a CD8-40L fusion protein, a trimeric form of CD40L comprising CD40L molecules having a modified leucine zipper covalently attached to said CD40L molecules, anti-CD40 antibodies, cells that express CD40L, lipopolysaccharide (LPS) and polyI/C; and
isolating the dendritic cell.

80. The method according to claim 79, wherein contacting the dendritic cell with the antigen comprises contacting the dendritic cell with cells derived from a graft or transplant donor.

81. The method according to claim 79, wherein the peripheral blood monocytes are derived from the graft or transplant recipient.